

Adult-type rhabdomyoma of the larynx: clinico-pathologic study of an uncommon tumor in a rare location

Short title: Adult-type rhabdomyoma of the larynx

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Abstract

Rhabdomyoma is an uncommon benign mesenchymal tumor with skeletal muscle differentiation that may occur either in the heart or in extra-cardiac sites. Even though the head and neck region is the most common area of extra-cardiac rhabdomyoma, the larynx is rarely involved. We present the case of an 85-year-old woman who reported a 10-day history of breathing difficulties, dysphagia and dysphonia. A computed tomography scan of the head and neck showed a contrast-enhanced, solid hypopharyngeal-laryngeal neoplasm with well-defined margins causing subtotal obliteration of the right pyriform sinus and a reduction in air lumen of the laryngeal vestibule. The patient underwent complete endoscopic removal of the lesion; histologic examination revealed an adult-type rhabdomyoma based on the histologic features and the immunoreactivity of the neoplastic cells for desmin, myoglobin and muscle-specific actin but not for cytokeratin, S-100, CD68R, chromogranin-A and synaptophysin. Since clinical and imaging features are not specific for rhabdomyoma, histologic examination and immunohistochemical analyses play a central role in the differential diagnosis of the adult-type rhabdomyoma from other laryngeal neoplasms. A correct diagnosis is mandatory to avoid inappropriate treatment.

Keywords: rhabdomyoma, laryngeal tumor, immunohistochemistry, differential diagnosis

Introduction

Rhabdomyoma (RM) is an uncommon benign mesenchymal tumor showing skeletal muscle differentiation that may occur in cardiac and extra-cardiac locations [1]. Cardiac RM is considered an hamartomatous lesion that usually occurs in children with phakomatosis, such as tuberous sclerosis. In contrast, extra-cardiac RM is usually sporadic and may present at all ages. Depending on the degree of differentiation and the site of development, extra-cardiac RM is classified into foetal-, adult- and genital-type [1-3]. The foetal-type exhibits immature skeletal muscle differentiation and typically occurs as a solitary lesion in children. The adult-type RM exhibits mature skeletal muscle differentiation, occurs in adulthood with a median age of 60 years and is usually, but not invariably, solitary. The genital-type RM shows an advanced degree of skeletal muscle differentiation and typically presents as a solitary lesion in the vagina, vulva and cervix and, rarely, in the paratesticular region and epididymis of middle aged patients. In terms of molecular genetics, both adult- and foetal-type RM have been associated with basal cell naevus syndrome and activation of the sonic hedgehog pathway [4, 5]. A t(15;17) (q24;p13) has been reported in one case of adult-type RM [6].

Even though the head and neck region is the most common area of extra-cardiac RM [1-3], this tumor is extremely rare in the larynx [7-38]. For this reason, we describe the clinico-pathologic features of an adult-type RM of the larynx diagnosed in an 85-year-old woman and review the pertinent literature with the specific aim to assess the diagnostic and therapeutic standards for this uncommon tumor that are invariably necessary to avoid erroneous diagnosis and inappropriate treatment.

Case Presentation

An 85-year-old woman was referred to our institution with a 10-day history of breathing difficulties, dysphagia for solids and liquids and dysphonia. The patient was a former smoker (20

cigarettes/day for 45 years until the age of 60), while no alcohol intake was reported. Patient's medical history was positive for chronic obstructive pulmonary disease, hypertension, anaemia, osteoporosis, goitre, and chronic renal failure.

General otolaryngological examination was normal. Endoscopy revealed a submucosal lesion in the right arytenoid, covered with normal mucosa, extending towards the right piriform sinus. The right vocal cord appeared fixed while the left was hypomobile, thus reducing breathing space. There was no clinical evidence of cervical lymphadenopathy. A computed tomography (CT) scan of the head and neck showed a contrast-enhanced, solid hypopharyngeal-laryngeal neoplasm with well-defined margins, originating from the right piriform sinus with partial contralateral extension. The mass measured 18x22x12 mm and extended caudally to the right arytenoid and the upper margin of the cricoid cartilage, causing subtotal obliteration of the right pyriform sinus and a reduction in air lumen of the laryngeal vestibule. Other laryngeal structures were preserved (*Figure 1*).

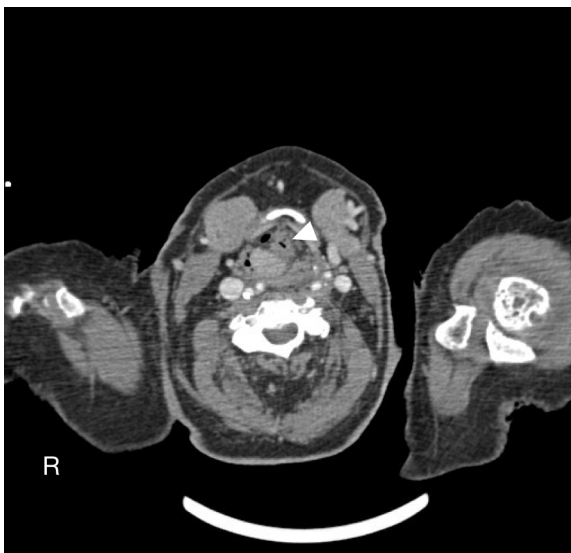


Figure 1: Contrast-enhanced computed tomography scan of the neck shows a large (18x22x12 mm) solid hypopharyngeal-laryngeal mass with well-defined margins, originating from the right piriform sinus with partial contralateral extension (white arrow).

The patient underwent complete endoscopic removal of the lesion and temporary tracheostomy for respiratory distress; tracheostomy was closed 30 days later. Neither post-operative complications nor signs of recurrence during a 18-month follow-up were observed.

Histologic examination of the neoplasm revealed a well circumscribed, not encapsulated, proliferation of large closely packed neoplastic round to polygonal cells in a scant stroma (*Figure 2, A and B*). The cells showed a deeply eosinophilic focally vacuolated cytoplasm and round, predominantly central, nuclei, at times with prominent nucleolus. In some cells, multiple nuclei were found. Cells with a peripheral cytoplasmic clear zone traversed by thin cytoplasmic strands extending from the more central acidophilic cytoplasm to the periphery (so-called “spider” cells) were detected as well. Mitotic activity and necrosis were absent. Neoplastic cells were immunoreactive for Desmin (*Figure 2C*), Myoglobin (*Figure 2D*) and Muscle Specific Actin. Immunohistochemical staining for cytokeratin (CKAEAE3 and CKMNF116), S100 protein, CD68R, Chromogranin-A and Synaptophysin failed to stain the neoplastic cells. Based on the histologic and immunohistochemical features, a diagnosis of adult-type RM of the larynx was made.

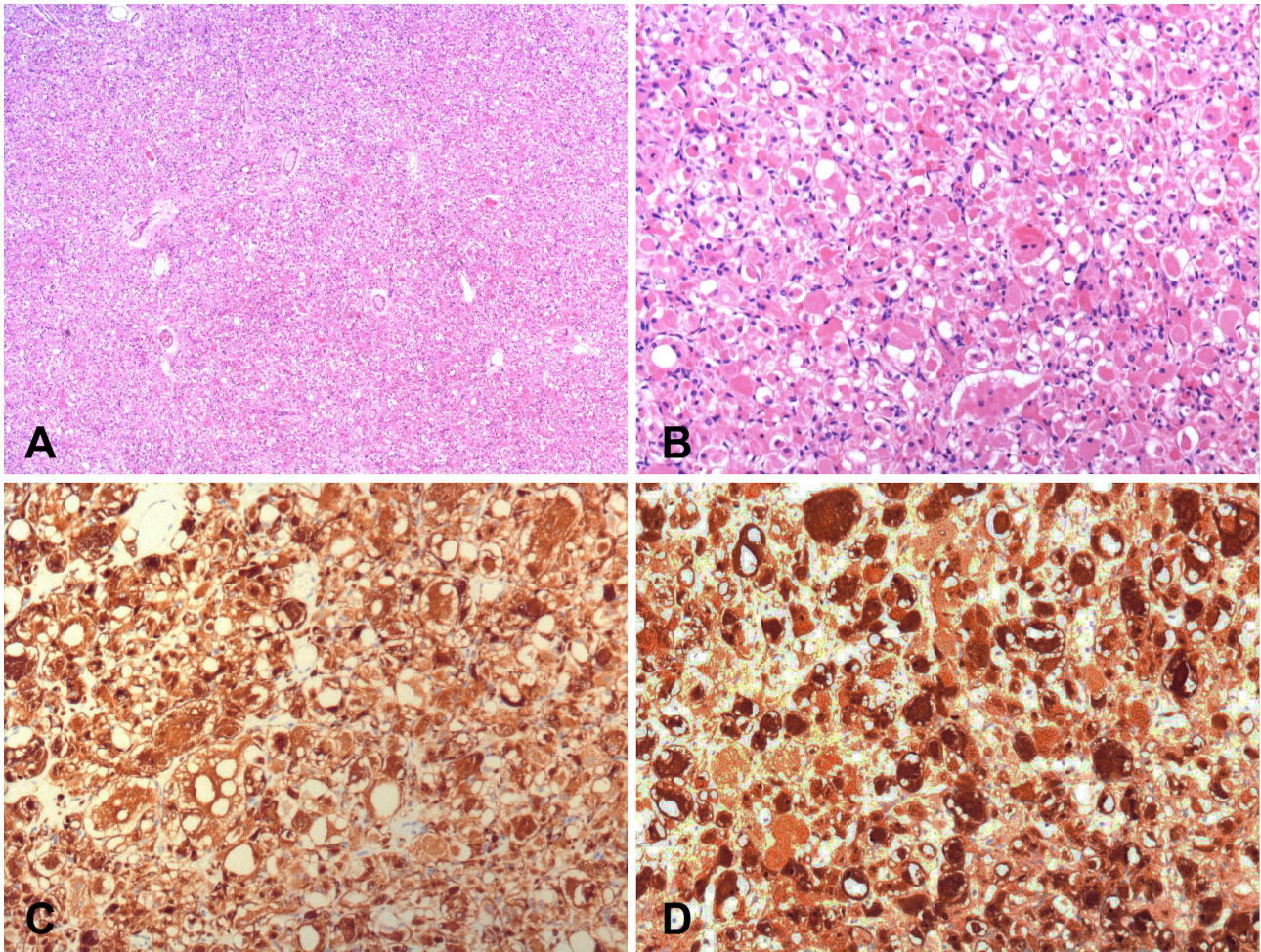


Figure 2: Low- and high-power magnification of tumor sections stained with Haematoxylin and Eosin are illustrated in A and B, respectively. The neoplastic cells are diffusely positive for Desmin (C) and Myoglobin (D).

Discussion

About 90% of extra-cardiac RMs occur in the head and neck region [1-3, 17]. Even though usually solitary, multifocal lesions have been described as well [27, 34]. Pharynx and oral cavity are the most commonly involved sites, while the larynx is an extremely rare location. Only twenty-three well-documented cases of RM of the larynx were reported in a review of the literature published in 1995 by Johansen; of these, 12 were adult-type laryngeal RM, 3 were adult-type multifocal RM, 4 were foetal cellular RM and 4 were foetal myxoid RM [21]. Since then, no more than twenty other cases of adult-type RM have been published. A comprehensive list of adult-type laryngeal RMs reported in the literature is summarized in Table 1.

Table 1

Ref.	Age/Gender Location	Chief Complaint Duration of Symptoms	Treatment
7	48/M R vocal fold	Hoarseness 3 months	Endoscopic excision
8	55/M L transglottic area	Hoarseness 3 years	Laryngofissure Local excision
9	52/F R false vocal fold	Hoarseness 3 years	Endoscopic excision
11	55/M R false vocal fold	NA	Endoscopic excision
12	64/F R ventricle	Hoarseness, foreign-body sensation 6 months	Endoscopic excision
13	39/M Vocal fold	Hoarseness 3 years	Endoscopic excision
14	76/F L true vocal fold	Hoarseness 2 months	Endoscopic excision
15	16/M R transglottic area	Acute airway obstruction Sudden onset	Tracheotomy Total laryngectomy
17	52/M L vocal fold	Hoarseness 6 months	Lateral pharyngotomy
17	66/M R vocal fold	Hoarseness 8 years	Excision
18	51/F Both arytenoid cartilages	Dyspnoea, dysphagia NA	External removal
21	51/M L ventricular fold	Hoarseness, snoring 1 year	Hemilaryngectomy
22	64/M L aryepiglottic fold	R asymptomatic submandibular mass	Cervical approach and L lateral pharyngotomy
23	69/F Vocal fold	Hoarseness 5 years	Endoscopic excision
24	39/M L-sided paraglottic space	Dysphagia and weight loss 5 months	Resection
25	66/M Arytenoid	Hoarseness and dysphagia 4 months	External removal
26	79/M R false vocal fold	Hoarseness 5 years	External removal
27	69/M Epiglottis (multifocal)	R asymptomatic submandibular mass	External removal
28	35/M Extrinsic laryngeal muscles	Cervical bulging NA	Resection
29	66/M R arytenoid	Dysphagia and hoarseness 3 years (sudden dyspnea)	Endoscopic excision
30	72/F L aryepiglottic fold (multifocal)	Globulus and hoarseness 1 year	Endoscopic excision
31	50/F R glossoepiglottic fold and vocal fold	NA	Exeresis with CO ₂ laser
32	76/M Arytenoid	Hoarsness, dysphagia and sleep-apnoea NA	Multiple endoscopic multiple debulking procedures
33	NA/NA Glottis	Dysphonia NA	Endoscopic excision
34	55/M L paraglottic space (multifocal)	Hoarseness and slight dysphagia 3 months	Endoscopic excision
35	35/M L supraglottic space	Hoarseness 1 year	Endoscopic excision
36	67/F Supraglottis	Hoarseness and progressive dyspnea NA	Hemilaryngectomy
37	50/M R aryepiglottic fold	Change in voice 2 years	Total laryngectomy
38	75/M	Hoarsness	Endoscopic excision

	R vocal fold	4 years	
Present	85/F	Sudden breathing difficulties, dysphagia	Endoscopic excision
Case	R arytenoid	10 days	

Table 1: Clinical comparative synopsis of our case with the other cases of adult-type RM of the larynx reported in the literature, including present case. R: right. L: left. NA: not available.

In the larynx, adult-type RM usually occurs as solitary lesion in adulthood, is more frequent in men than in women and more frequently involves the glottic and supraglottic regions [7-38]. In our case, the oldest patient in which an adult-type RM has been reported, the tumor involved primarily the arytenoid, an uncommon site of development for this neoplasm [18, 24, 28, 29, 31]. These tumors grow slowly as a submucosal painless swelling that progressively leads to hoarseness, foreign-body sensation, dysphagia and dyspnea [3, 21]. Even though the duration of symptoms is usually long (typically years), airway obstruction and dyspnea may develop suddenly [15, 19]. In our case, the patient presented with a 10-day history of breathing difficulties, dysphagia for solids and liquids and dysphonia. Imaging findings usually suggest a benign lesion because of submucosal location and absence of invasion of surrounding soft tissues. However, in particular on CT scan, adult-type RM may mimic malignant tumors because of indistinct borders blending into adjacent isodense muscles [24]. Thus, the absence of specific clinical and of unequivocal imaging features contributes to make any single case a diagnostic challenge. Pre-operative differential diagnosis includes cysts, benign tumors (i.e., hemangioma, lipoma, neurofibroma, and granular cell tumor) and malignant neoplasms (i.e., squamous cell carcinoma, rhabdomyosarcoma).

Definitive diagnosis is possible only after histologic examination and immunohistochemical analysis. It is recommended to obtain the neoplastic tissue by excisional rather than incisional biopsy because in the latter the small amount of tumor tissue may contribute to misdiagnosis and inappropriate treatment [15, 37]. Independently of the site of the tumor, the histology of adult-type RM is quite distinctive [1]. As in our case, adult-type RM is composed by dense sheets of closely packed large, round cells with eosinophilic and granular cytoplasm, and

centrally or peripherally located nuclei, in part with prominent nucleoli. Many cells are vacuolated because of intra-cellular glycogen that dissolves during processing. However, since these findings may resemble a variety of other lesions, in particular granular cell tumor, hibernoma and paraganglioma, immunohistochemical staining is required for diagnosis. Neoplastic cells of adult-type RM – as reported in this case - are immunoreactive for Desmin, Myoglobin and Muscle Specific Actin (markers of differentiated skeletal muscle cells) and negative for cytokeratin, S100, CD68R and neuroendocrine marker (Synaptophysin and Chromogranin-A).

The treatment of adult-type RM is surgical and can be done either by endoscopic or external approach, but always preserving the adjacent structures such as the vocal folds and the swallowing apparatus. Complete surgical excision is curative. Adult-type RMs may recur [3, 13, 18], especially after incomplete excision; however, aggressive behavior and malignant transformation have never been described.

In conclusion, the adult-type RM of the larynx is a very rare benign tumor that must be distinguished from other submucosal laryngeal neoplasms. The present case fulfills the clinicopathologic criteria for the diagnosis of adult-type RM of the larynx. Since clinical and imaging features are not specific for adult-type RM, histology and immunohistochemistry are mandatory for a definitive diagnosis. Radical endoscopic excision is the recommended procedure to obtain tissue for histologic evaluation and for patient treatment.

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